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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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KNOBBE MARTENS OLSON & BEAR LLP
2040 MAIN STREET
FOURTEENTH FLOOR
IRVINE, CA 92614

EXAMINER	
ROMEO, DAVID S	
ART UNIT	PAPER NUMBER
1647	

SHORTENED STATUTORY PERIOD OF RESPONSE	NOTIFICATION DATE	DELIVERY MODE
3 MONTHS	02/27/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Notice of this Office communication was sent electronically on the above-indicated "Notification Date" and has a shortened statutory period for reply of 3 MONTHS from 02/27/2007.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

jcartee@kmob.com
eOAPilot@kmob.com

Office Action Summary	Application No.	Applicant(s)	
	10/063,617	GODDARD ET AL.	
	Examiner	Art Unit	
	David S. Romeo	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 November 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6-8 and 11-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6-8 and 11-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1106*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/09/2006 has been entered.

Claims 6–8 and 11–17 are pending and being examined.

Maintained Formal Matters, Objections, and/or Rejections:

Claim Rejections - 35 USC §§ 101, 112

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6–8 and 11–17 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

Applicants incorporate by reference their previously submitted arguments, and for the reasons of record assert that the specification contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented and therefore must be taken as sufficient to satisfy the utility requirement of 35 U.S.C. § 101. Applicants also submit that for reasons of record, the PTO has not met its burden of providing evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility. Applicants argue that even if the PTO has

met its initial burden, Applicants' rebuttal evidence previously submitted and additional evidence submitted herewith is sufficient to prove that it is more likely than not that a person of skill in the art would be convinced, to a reasonable probability, that the asserted utility is true; that Applicants' evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility; that even if the correlation between Applicants evidence and the asserted utility is not exact, such that there are exceptions to the correlation between the evidence and the asserted utility, this is sufficient to establish a utility, citing Fujikawa v. Wattanasin, 93 F.3d 1559, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996) (stating that "a 'rigorous correlation' need not be shown in order to establish practical utility; 'reasonable correlation' suffices," and thus a utility was established even though there were exceptions to the correlation between the disclosed in vitro data and asserted in vivo utility); that exceptions between the evidence disclosed and the asserted utility is permissible; that the standard is not absolute certainty; that in light of all of the evidence, the PTO's arguments are not adequate to support the utility rejection of the claimed invention under 35 U.S.C. § 101.

Applicants argue that in Application No. 10/063,529, No. 10/063,530, No. 10/063,524, No. 10/063,582, and No. 10/063,583 filed by Applicants that rely on data from the exact same disclosure, Example 18, and in which the Applicants have submitted substantially the same references in support of their asserted utility, the PTO has concluded that one of skill in the art would find it more likely than not that an increase in message as measured by RT-PCR would be predictive of an increase in protein expression levels. Applicants request that the Examiner recognize the utility of the claimed invention, supported by the data presented in Example 18 and the numerous cited references, as was done in the other applications referenced above.

Applicants' arguments have been fully considered but they are not persuasive. Suffice it to say that each case must be decided on its own merits based on the evidence of record.

Applicants argue that the gene expression data provided in Example 18 of the present application are sufficient to establish that the PRO1753 gene is differentially expressed in esophageal tumor tissue as compared to normal esophageal tissue, and is therefore useful as a diagnostic tool for esophageal cancer; that this assertion is based on the results of RT-PCR analysis of pooled normal esophageal tissue and pooled esophageal tumor tissue using methods that are well-established in the art; that this utility is substantial, i.e. distinguishing tumor cells from normal cells is not an insubstantial or trivial utility without a real world use, and it is specific, i.e. it is directed to specific disease and is not a utility that the entire class of nucleic acids shares; that this asserted utility is credible, as one of skill in the art would readily believe that a nucleic acid sequence can be used as a marker to distinguish tumor tissue from normal tissue. Applicants remind the Examiner that Applicants enjoy a presumption that their assertions are true; that the Examiner must approach Applicants' assertion of utility as being sufficient to satisfy the utility requirement; that with respect to the use of the PRO1753 nucleic acid to distinguish tumor from normal tissue, the Examiner must accept this assertion as true "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility;" that the question is whether the PTO has established that there is a reason to doubt the objective truth of Applicants' assertion that using standard RT-PCR procedures to examine the expression of the PRO1753 mRNA in pooled normal esophageal samples and pooled esophageal tumor samples, Applicants discovered that PRO1753 mRNA is differentially expressed between normal and tumor such that it can be used as a diagnostic tool. Applicants' arguments have been

fully considered but they are not persuasive. As noted by applicants, "any inquiry must start by asking if there is any reason to question the truth of the statement of utility." As indicated previously, applicants rely on a general correlation between mRNA expression and expression of the encoded protein rather than the correlation between PRO1753 transcripts and PRO1753 polypeptide expression to argue that it is more likely than not that the change in PRO1753 transcripts is correlated with an assumed change in PRO1753 polypeptide expression. Without any evidence of PRO1753 polypeptide expression in either tumor tissue or normal tissue this argument is of no avail to Appellants because a commonly understood general rule or dogma amounts to a showing that it is "not implausible" that invention will work for its intended purpose, which, in the face of the countervailing evidence, is insubstantial evidence of utility for the PRO1753 polypeptide. The inherent lack of certainty in this general correlation results in a failure to prove practical utility for the PRO1753 polypeptide and antibodies.

Applicants argue that the PTO is arguing that because "high throughput technologies, such as DNA microarrays" produce differences in mRNA that are attributable to "disease-independent differences between samples," this establishes "a reason for one skilled in the art to question the objective truth" of Applicants' asserted utility which is based on RT-PCR analysis of pooled samples of normal and tumor tissue, not microarrays; that one of skill in the art would not accept that the PTO has established a basis to doubt Applicants' asserted utility; that those of skill in the art recognize that RT-PCR is a more accurate and reliable technique than microarrays, citing Kuo (Proteomics 2005; 5(4):894-906, ABSTRACT ONLY provided); that it would be readily apparent to one skilled in the art that opinions regarding data from high-throughput techniques such as microarrays are simply not relevant to Applicants' RT-PCR data, and are not

a reason to doubt the truth of Applicants' asserted utility; that even if accurate, a point which Applicants do not concede, Hu's and LaBaer's opinions regarding microarray studies are not relevant to the utility of the instant application which does not rely on microarray data. Applicants emphasize that they are not asserting that microarray data are not reliable (that is apparently the PTO's position based on Hu and LaBaer), merely that Applicants are using a method that is recognized by those of skill in the art as more reliable and sensitive. Applicants argue that the PTO's argument misses the point of Applicants' reliance on Kuo; that Kuo is cited as evidence to support Applicants' assertion that Applicants' PCR data are more accurate and reliable than the microarray technique commented on by Hu and LaBaer; that Kuo supports this assertion because it is evidence that one of skill in the art would regard PCR as a more accurate and reliable method of assessing changes in mRNA; that whether or not the microarray technique commented on by Hu and LaBaer yields "disease-independent" results is not relevant to Applicants' data because, as evidenced by Kuo, PCR data such as Applicants' are more accurate and reliable than the microarray data relied on by Hu and LaBaer; that until the PTO provides evidence that transcript changes detected by PCR analysis of pooled normal and tumor samples are often "disease-independent," the PTO's rejection of the data in Example 18 based on Hu and LaBaer is misplaced, and Applicants' asserted utility must be presumed true. Applicants' arguments have been fully considered but they are not persuasive. The gist of applicants' argument is that Hu and LaBaer rely on microarray data, Kuo teaches that RT-PCR is a more accurate and reliable technique than microarrays, therefore Hu and LaBaer are not relevant because microarray data are inaccurate and unreliable, as compared to RT-PCR data. However, it cannot be determined from Kuo's abstract if the fold change results from microarray

experiments correlate closely, or not, with results from assays like quantitative reverse transcription PCR. Therefore, applicants' reliance on Kuo is misplaced. Hu and LaBaer are relevant because genes whose modest changes in expression may be unrelated to the disease cannot be used as a disease marker because the change is unrelated to the disease.

Applicants argue that neither Hu nor LaBaer cite any references to support their assertions that "most [microarray differences] are attributable to disease-independent differences between the samples" and that "it is not always clear if [the microarray differences] are biologically meaningful;" that in the absence of any supporting references, Applicants cannot independently evaluate these statements to determine what is meant by "disease-independent differences" and "biologically meaningful;" that read in light of the entire article and accompanying letter to the editor, Applicants assert that these statements should be interpreted to mean that the observed differences do not play a role in the development or progression of the disease state, or that such a role in the disease state has not yet been published; that a differentially expressed mRNA can serve as a marker of a disease even if it is "disease-independent" in the sense that it has no role in the cause or progression of a disease, or if any such role is not yet published in the literature. Applicants invite the PTO to provide support for an alternate interpretation of "disease-independent" as used in Hu and LaBaer. Applicants' arguments have been fully considered but they are not persuasive.

LaBaer states:

> In the accelerating quest for disease biomarkers, the use of high-throughput technologies, such as DNA microarrays and proteomics experiments, has produced vast datasets identifying thousands of genes whose expression patterns differ in diseased versus normal samples. Although many of these differences may reach statistical significance, they are not always biologically meaningful. For example, reports of mRNA or protein changes of as little as two-fold are not

> uncommon, and although some changes of this magnitude turn out to be important, most are attributable to disease-independent differences between the samples. *See first paragraph.*

Applicants argue that the PTO presents no evidence to support the assertions with respect to Applicants' arguments that Hu and LaBaer are silent regarding the reliability of pooled samples, which are incorporated herein by reference; that the PTO uses conclusory and unsupported arguments as the basis for dismissing the declaration of an expert; that the PTO's position is inconsistent with the Utility Examination Guidelines which state, "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered" and also is inconsistent with the requirement of the PTO to support its assertions of fact, citing In re Zurko, 258 F.3d 1379, 1385, 59 USPQ2d 1693, 1697 (Fed. Cir. 2001); that absent supporting evidence, it is inappropriate for the PTO to dismiss Applicants' arguments and Mr. Grimaldi's opinion regarding pooled samples simply because the PTO wishes to take a contrarian position on the use of pooled samples in diagnostics; that that applicants' expert has established that "[d]ata from pooled samples is more likely to be accurate than data obtained from a sample from a single individual," citing first Grimaldi Declaration at ¶5; that the Grimaldi declaration make clear that, in fact, "the results of the gene expression studies indicate that the genes of interest can be used to differentiate tumor from normal," citing first Grimaldi Declaration at ¶7. Applicants refrain from further rebutting the PTO's assertions because there presently are no facts on the record to support a position other than that of Mr. Grimaldi's. Applicants respectfully request that the PTO provide evidentiary support for its assertions regarding pooled samples in order to fully develop these issues under

examination. Applicants argue that Applicants do not know how to respond to the PTO's statement that the first Grimaldi declaration is "in contrast with the specification's teachings," since the Office has not explained how the declaration is in contrast with the quoted portion of the specification or what relevance any contrast between the two statements has to Applicants' asserted utility; that the Office's statement that "Hu is evidence that a skilled artisan would consider the precise level of PRO1753 gene expression as relevant" is not supported by any reasoning or citation to Hu; that Applicants' are unaware of any teaching in Hu regarding the need for a "precise level of PRO1753 gene expression" to use it as a molecular marker to distinguish tumor tissue from normal tissue; that Hu and LaBaer teach nothing at all regarding developing diagnostic markers of cancer; that the evidence reported in Example 18, supported by the first Grimaldi Declaration, establish that there is at least a two-fold difference in PRO1753 mRNA between esophageal tumor tissue as compared to normal esophageal tissue; that Applicants' assertion that PRO1753 mRNA can be used to distinguish esophageal tumor tissue from normal esophageal tissue must be presumed true by the Examiner unless there is a reason that one of skill in the art would doubt the objective truth of Applicants' statements; that Applicants have shown that the references by Hu and LaBaer are inapplicable to Applicants' RT-PCR data, and the PTO has provided no evidentiary basis for dismissing the Grimaldi Declaration; that any challenge to the sufficiency of the data with respect to the utility of the nucleic acid is inappropriate; that the only issue which remains is whether the data in Example 18 regarding differential expression of the PRO1753 mRNA are reasonably correlated with differential expression of the PRO1753 polypeptide such that the claimed polypeptides have utility as diagnostic tools as well; that even if the PTO has established a reasonable doubt

regarding Applicants' assertion that they are reasonably correlated, Applicants' overwhelming rebuttal evidence is more than sufficient to establish that changes in mRNA level lead to corresponding changes in protein level. Applicants' arguments have been fully considered but they are not persuasive. Firstly, pooled samples eliminate the effect of variation on applicants' conclusion regarding differential PRO1753 mRNA expression. However, pooled samples do not eliminate the variation itself. Without knowledge of the degree of variation within the pool one would not know if any particular measurement from a tissue would indicate normal tissue or tumor tissue and would not know if normal tissue could be distinguished from tumor tissue. The examiner believes that he has adequately supported his arguments.

Secondly, the first Grimaldi declaration states that the DNA libraries used in the gene expression studies were made from pooled samples of normal and of tumor tissues. This is in contrast to the specification, which teaches that differential expression of PRO polypeptide-encoding nucleic acids in one or more tumor tissues as compared to one or more normal tissues of the same tissue type (page 140, paragraph 0350).

Thirdly, applicants are the ones that argued, and continue to argue, that the "precise" level of gene expression is irrelevant:

> "[t]he precise levels of gene expression are irrelevant; what matters is that there is a relative difference in expression between normal tissue and tumor tissue." First Grimaldi Declaration at ¶ 7.

> This declaration makes clear that since it is the relative level of expression between normal tissue and suspected cancerous tissue that is important, how high the level of expression in normal tissue is, is irrelevant. Appeal brief filed 12/27/2005, at page 17.

However, Hu and LaBaer are evidence that a skilled artisan would consider "precise levels of gene expression," "relative difference in expression," or "how high the level of expression" as relevant.

Applicants argue that it is well-established in the art that a change in the level of mRNA encoding a particular protein generally leads to a corresponding change in the level of the encoded protein; that given Applicants' evidence of differential expression of the mRNA for the PRO 1753 polypeptide in esophageal tumors, it is likely that the PRO1753 polypeptide is also differentially expressed; that proteins differentially expressed in certain tumors have utility as diagnostic tools; that the Examiner should approach these assertions of utility with a presumption that they are true; that Applicants have previously discussed at length why the Haynes reference is not relevant to the issue of whether differential mRNA expression levels for a particular gene lead to corresponding differential expression of the encoded protein; that Applicants incorporate by reference the previous arguments, and will not repeat them here; that Haynes, and similar references, looked for a correlation between the level of mRNA and corresponding protein by plotting a single measurement of mRNA level vs. protein level for a large group of different genes; that the only way that such a plot would result in a significant correlation is if there exists a global ratio between mRNA levels and protein levels common across all genes, i.e., that for every X copies of an mRNA, there are Y copies of the encoded protein, such that the ratio of X:Y is constant across all genes; that if such a global ratio existed, then plotting mRNA levels for different genes against their corresponding protein levels would result in a strong correlation; that, for example, if the global ratio is 2:1, then 100 transcripts of gene X would result in about 50 copies of protein X, 500 transcripts of gene Y would result in about 250 copies of protein Y,

and 1000 transcripts of gene Z would result in about 500 copies of protein Z; that plotting the amount of mRNA against the amount of protein for these different genes in a sample would result in a strong correlation; that this is what Haynes and similar references examined; that according to the PTO, they did not find a strong correlation; that this is because the ratio between transcript copy number and protein level is apparently not the same for all genes; that as a result of these findings, Haynes concluded that protein levels cannot be accurately calculated from mRNA levels, and that "it is evident that the analysis of mature protein products in cells is essential as there are numerous levels of control of protein synthesis, degradation, processing and modification." Haynes at 1863, right column, full paragraph 2; that regardless of whether this conclusion is correct or not, it is not contrary to Applicants' assertion, and is not relevant to the question of whether differential mRNA levels for a particular gene lead to corresponding differential expression of the encoded protein; that in contrast, Applicants' asserted utility does not require knowledge of, or even the existence of, a global ratio between mRNA levels and protein levels; that nor do Applicants' assertions require calculation of protein levels based on measured mRNA levels; that unlike Haynes, Applicants are not relying on a single measure of mRNA for a particular gene and then attempting to calculate protein levels based on a global ratio between mRNA and protein levels; that instead, Applicants are relying on differential mRNA expression, where mRNA levels are measured in two different conditions, i.e. tumor and normal; that a difference in mRNA expression level for a particular gene typically leads to a corresponding difference in the expression level of the encoded protein, citing the first Grimaldi Declaration at paragraph 7; that the Haynes reference, and similar studies, are applicable only to a completely unrelated issue - whether a single measure of mRNA levels can be used to predict

protein levels - and therefore, none of the data or conclusions of these references have any bearing on Applicants' assertions; that the PTO repeatedly relies on the assertion that the skilled artisan would not know if or how expression of the PRO1753 polypeptide would change in tumors because there are numerous levels of control of protein synthesis, degradation, processing, and modification, that are only apparent by direct protein analysis; that this assertion is based on a statement in Haynes; that however, as discussed above, the authors of Haynes based their conclusions on a lack of a global relationship between mRNA levels and protein levels across different genes; that this is not relevant to the question of whether one of skill in the art would expect changes in mRNA level to lead to changes in protein level; that the authors of Haynes did not address this question, and their statements regarding the ability to calculate protein levels based on mRNA levels refer only to their experiments looking for a global correlation.

Applicants argue that PTO is not considering the entire teachings of Molecular Biology of the Cell, 3rd ed., Molecular Biology of the Cell, 4th ed., Genes VI, the Polakis Declaration, and Meric and chooses to ignore portions of the text which support Applicants; that each of these references support Applicants' position when read in their entirety is of record, and will not be repeated here.

Applicants argue that even if one acknowledges that there are numerous levels of control of protein synthesis, degradation, processing and modification, this is still not contrary to Applicants' assertion that when mRNA levels for a particular gene are changed, there is generally a corresponding change in protein levels; that just because a cell has numerous means of modulating protein levels, this does not prohibit the possibility that a change in mRNA level

generally results in change in protein level - these are not mutually exclusive propositions; that one must look at actual experiments where a change in mRNA level was assessed to determine if the change generally results in a corresponding change in protein levels; that none of the references cited by the PTO teach to the contrary, and Applicants' evidence discussed below teaches that this is in fact the case; that Applicants have shown that the references such as Haynes that examine mRNA/protein relationships across different genes are simply not relevant to the issue of whether a change in mRNA levels leads to a corresponding change in the level of the encoded protein; that the other references relied on by the PTO support Applicants' position when read in their entirety; that taken together, the PTO's arguments are not sufficient to satisfy the burden to "provide[] evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility," citing In re Brana, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995).

Applicants' arguments have been fully considered but they are not persuasive. Applicants are not comparing mRNA changes in the same cell. Applicants are comparing mRNA expression in a normal cell with mRNA expression in a tumor cell. Applicants have not tested PRO1753 polypeptide expression. The fact that there may be a commonly understood general rule or dogma that increased mRNA levels are predictive of corresponding increased levels of the encoded protein does not establish the correlation between the change, if any, in PRO1753 transcripts and PRO1753 polypeptide expression in tumors because there are examples of genes for which such a correlation does not exist, according to Dr. Polakis.

Applicants argue that the details of the previously submitted second Declaration by J. Christopher Grimaldi, a copy of a declaration of Paul Polakis, Ph.D., excerpts from the

Molecular Biology of the Cell, a leading textbook in the field (Bruce Alberts, et al., Molecular Biology of the Cell (3r° ed. 1994) and (4th ed. 2002), excerpts from the textbook, Genes VI, (Benjamin Lewin, Genes VI (1997)), a reference by Zhigang et al., World Journal of Surgical Oncology 2:13, 2004, a reference by Meric et al., Molecular Cancer Therapeutics, vol. 1,971-979 (2002), over 100 additional references in support of their assertion that changes in mRNA for a particular gene are positively correlated to changes in the corresponding protein level, and a second declaration by Dr. Polakis and how they support Applicants' asserted utility, are of record and will not be repeated here.

Applicants submit herewith a copy of a declaration by Randy Scott, Ph.D. (attached as Exhibit 1). Applicants argue that Dr. Scott is an independent expert in the field of molecular diagnostics, with over 15 years experience; that he is the author of over 40 scientific publications in the fields of protein biology, gene discovery, and cancer, and is an inventor on several issued patents; that his curriculum vitae is attached to the declaration; that in paragraph 10 of his declaration, Dr. Scott states: "One reason for the success and wide-spread use of the DNA microarray technique, which has led to the emergence of a new industry, is that generally there is a good correlation between mRNA levels determined by microarray analysis and expression levels of the translated protein. Although there are some exceptions on an individual gene basis, it has been a consensus in the scientific community that elevated mRNA levels are good predictors of increased abundance of the corresponding translated proteins in a particular tissue. Therefore, diagnostic markers and drug candidates can be readily and efficiently screened and identified using this technique, without the need to directly measure individual protein expression levels." Scott Declaration at ¶10. Applicants argue that Dr. Scott also states that,

contrary to the contentions of the PTO, diagnostic markers can be identified "without the need to directly measure individual protein expression levels;" that this opinion is supported by Dr. Scott's extensive experience in the field, as well as the fact that an entire industry has developed around technology to assess differential mRNA expression; that there would be little reason to study changes in mRNA expression levels if those changes did not result in corresponding changes in the encoded protein levels; that the case law has clearly established that in considering affidavit evidence, the PTO must consider all of the evidence of record anew. Applicants also respectfully draw the PTO's attention to the Utility Examination Guidelines which state, "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered." Applicants argue that applicants have submitted herewith additional expert Declarations in addition to the declarations and over 115 references already of record, which support Applicants' asserted utility, either directly or indirectly; that this evidence supports the assertion that in general, a change in mRNA expression level for a particular gene leads to a corresponding change in the level of expression of the encoded protein; that as Applicants have previously acknowledged, the correlation between changes in mRNA level and protein level is not exact, and there are exceptions; that however, Applicants remind the PTO that the asserted utility does not have to be established to a statistical certainty, or beyond a reasonable doubt; that therefore, the fact that there are exceptions to the correlation between changes in mRNA and changes in protein does not provide a proper basis for rejecting Applicants' asserted utility; that considering the evidence as a whole, with the overwhelming majority of the evidence supporting Applicants'

asserted utility, a person of skill in the art would conclude that Applicants' asserted utility is "more likely than not true;" that applicants have offered sufficient evidence to establish that it is more likely than not that one of skill in the art would believe that because the PRO 1753 mRNA is differentially expressed in esophageal tumor tissue as compared to normal esophageal tissue, the PRO1753 polypeptide will likewise be differentially expressed; that this differential expression of the PRO1753 polypeptide makes the claimed polypeptides useful as diagnostic tools for cancer, particularly esophageal cancer. Applicants' arguments have been fully considered but they are not persuasive. The declaration under 37 CFR 1.132 filed by Randy Scott is insufficient to overcome the rejection of claims 6–8 and 11–17. Dr. Scott bases his conclusions on microarray data, which applicants have disparaged as inaccurate, unreliable, and insensitive. Further, Dr. Scott does not provide any data concerning PRO1753 mRNA expression, PRO1753 polypeptide expression, or the correlation between the two in any type of tissue sample. The fact that there may be a commonly understood general rule or dogma that increased mRNA levels are predictive of corresponding increased levels of the encoded protein does not establish the correlation between the change, if any, in PRO1753 transcripts and PRO1753 polypeptide expression in tumors because there are examples of genes for which such a correlation does not exist, according to first and second Polakis declarations and because there are some exceptions on an individual gene basis, according to the Scott declaration. Neither the specification nor any of applicants' arguments or other evidence establish if the disclosed change in PRO1753 mRNA expression is one of those cases where this is a correlation between a change in mRNA level and a corresponding change in the level of the encoded protein. Therefore, there is no reason for a skilled artisan to be reasonably convinced that the PRO1753 polypeptide will

exhibit the asserted diagnostic behavior. In the absence of any testing of the expression of the PRO1753 polypeptide, the specification does not provide some immediate benefit to the public for the PRO1753 polypeptide.

Applicants argue that the PTO takes the position that Applicants must present specific evidence directly demonstrating the utility of the claimed polypeptides; that this requirement is inconsistent with the Utility Guidelines and the courts; that the PTO implies the following argument: (1) the evidence of record demonstrates that there are exceptions to the general rule that increased mRNA levels correspond to increased levels of the encoded polypeptide; (2) because such exceptions exist, it is mandatory that specific data of differential PRO1753 polypeptide expression in esophageal tumor tissue as compared to normal esophageal tissue be disclosed; and (3) since such is not disclosed, the claimed polypeptides have no substantial utility; that adopting the PTO's standard for utility would result in a per se rule that a difference in mRNA expression cannot establish a utility for the encoded polypeptide and antibodies thereto; that the PTO chooses to heighten the utility requirement to require specific, direct evidence of utility when there are exceptions to a generally accepted rule that is relied upon for utility; that this heightened utility requirement is inconsistent with the Utility Guidelines and the courts; that there is no requirement that utility be dispositively proven; nor is there requirement that only direct evidence of utility is sufficient to establish utility; instead, it is established that indirect evidence that is reasonably indicative of utility is sufficient to fulfill the requirements of 35 U.S.C. §101, citing Nelson v. Bowler, 626 F.2d 853, 856; that furthermore, there is no requirement that indirect evidence necessarily and always prove actual utility; that there only need be a reasonable correlation between the indirect evidence and the asserted utility; that the

indirect evidence need not absolutely prove the asserted utility; that all that is required is that the tests be reasonably indicative of the asserted utility; that there need only be a sufficient correlation between the indirect evidence and the utility so as to convince those skilled in the art, to a reasonable probability, that the novel compound will possess the asserted utility; that the PTO appears to consider the above guidance from the courts inapplicable to the present situation because in those cases the claimed compound had been tested, and, in the present case, the claimed polypeptides have not been tested; that the PTO's position fails to recognize the issue in question for the above cases; that the issue in question was whether or not Appellants' evidence (in vitro or animal testing of compound), which was different in nature from the asserted utility (therapeutic use of compound), was sufficient to fulfill the requirements of 35 U.S.C. §101 when there was a reasonable link between Appellants' evidence and the asserted utility; that in the present case, Applicants submit that their evidence (differential mRNA expression) is reasonably linked to the asserted utility (diagnostic use of the encoded polypeptide); that insofar as it is uncontested that differential mRNA expression is reasonably linked to differential polypeptide expression, Applicants submit that such linkage is sufficient to fulfill the requirements of 35 U.S.C. § 101 as provided by the guidance of the Utility Guidelines and the courts; that Applicants' utility standard is the utility standard established by the PTO's guidelines based on the law as stated by the Courts, which is "more likely than not true," applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt," nor must an applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty, and evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true.

In summary, Applicants argue that the PTO's heightened requirement for establishing utility of the presently claimed polypeptides is contrary to the Utility Guidelines and the courts; that it is sufficient to present evidence of differential mRNA expression since it is understood in the art that differential mRNA expression is reasonably linked to differential polypeptide expression; that even if the PTO has presented evidence that changes in mRNA expression are not always correlated with changes in protein expression, Applicants' overwhelming rebuttal evidence is more than sufficient to establish that changes in mRNA level typically lead to corresponding changes in protein level; that as such, Applicants have established that it is more likely than not that one of skill in the art would believe that because the PRO1753 mRNA is differentially expressed in esophageal tumor tissue as compared to normal esophageal tissue, the PRO1753 polypeptide will likewise be differentially expressed in esophageal tumors; that the PTO has reached the same conclusion in other applications filed by Applicants that rely on data from the exact same disclosure, Example 18, and in which Applicants have submitted substantially the same references in support of their asserted utility; that when the evidence is applied to the proper standard for utility, it is clear that this differential expression of the PRO1753 polypeptide establishes the claimed polypeptides useful as diagnostic tools for cancer, particularly esophageal cancer.

Applicants' arguments have been fully considered but they are not persuasive. It is the examiner's position that applicants can choose to present as much or as little information in whatever form applicants see fit. Applicants have never been asked to prove the diagnostic utility of the claimed polypeptides. Unlike the situations wherein a claimed compound has been tested and has shown a pharmacological activity and therefore has a therapeutic utility sufficient

under the patent laws, or wherein an invention has only limited utility and is only operable in certain applications and therefore has some degree of utility sufficient for patentability, in the present situation Applicants have not provided any testing of PRO1753 polypeptide expression. The specification has not established if the disclosed change in PRO1753 mRNA expression is one of those cases where this is a correlation between a change in mRNA level and a corresponding change in the level of the encoded protein. Therefore, there is no reason for a skilled artisan to be reasonably convinced that the PRO1753 polypeptide will exhibit the asserted diagnostic behavior. In the absence of any testing of the expression of the PRO1753 polypeptide, the specification does not provide some immediate benefit to the public for the PRO1753 polypeptide. None of Applicants' exhibits, arguments or declarations establish if or how expression of the PRO1753 polypeptide changes in tumor tissue as compared to normal tissue. Instead, Applicants merely propose a utility that is "not implausible," relying on a general correlation between mRNA expression and expression of the encoded protein rather than the specific correlation between PRO1753 mRNA expression and PRO1753 polypeptide expression without any evidence of the expression level of the PRO1753 polypeptide in tumor tissue or normal tissue.

Applicants argue that the evidence of differential expression of the PRO1753 gene and polypeptide in certain types of tumor cells, along with the declarations and references discussed above, provide a specific utility for the claimed polypeptides. Applicants' arguments have been fully considered but they are not persuasive. Although the asserted utility may be specific to the claimed invention, it is not substantial. Therefore, the claimed invention lacks a specific and substantial asserted utility.

Applicants remind the PTO that the evidence supporting utility does not need to be direct evidence, nor does it need to provide an exact correlation between the submitted evidence and the asserted utility; that evidence which is "reasonably" correlated with the asserted utility is sufficient. See Fujikawa v. Wattanasin, 93 F.3d 1559, 1565, 39 U.S.P.Q. 2d 1895 (Fed. Cir. 1996) ("a 'rigorous correlation' need not be shown in order to establish practical utility; 'reasonable correlation' suffices"); Cross v. Iizuka, 753 F.2d 1040, 1050, 224 U.S.P.Q. 739 (Fed. Cir. 1985) (same); Nelson v. Bowler, 626 F.2d 853, 857, 206 U.S.P.Q. 881 (C.C.P.A. 1980) (same); that in addition, utility need only be shown to be "more likely than not true," not to a statistical certainty; that considering the evidence as a whole in light of the relevant standards for establishing utility, Applicants have established at least one specific, substantial, and credible utility; that the PTO has reached this conclusion in other applications filed by Applicants that rely on data from the exact same disclosure, Example 18, and in which the Applicants have submitted substantially the same references in support of their asserted utility; that in view of the above, Applicants respectfully request that the PTO reconsider and withdraw the utility rejection under 35 U.S.C. § 101.

The examiner believes he has responded to all pertinent arguments. The examiner incorporates by reference his responses to applicants previously submitted arguments incorporate by reference in applicants present response.

Claims 6–8 and 11–17 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial

asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Applicants argue that Applicants have established a substantial, specific, and credible utility for the claimed polypeptides; that to the extent that the enablement rejection is based on a lack of utility, Applicants respectfully request that the PTO reconsider and withdraw the enablement rejection under 35 U.S.C. §112.

As Applicants recognize, a rejection under § 112, first paragraph, may be maintained on the same basis as a lack of utility rejection under § 101. A deficiency under 35 U.S.C. 101 also creates a deficiency under 35 U.S.C. 112, first paragraph. If the application fails as a matter of fact to satisfy 35 U.S.C. § 101, then the application also fails as a matter of law to enable one of ordinary skill in the art to use the invention under 35 U.S.C. § 112. Obviously, if a claimed invention does not have utility, the specification cannot enable one to use it. As such, a rejection properly imposed under 35 U.S.C. 101 should be accompanied with a rejection under 35 U.S.C. 112, first paragraph. The 35 U.S.C. 112, first paragraph, rejection set out a separate rejection that incorporates by reference the factual basis and conclusions set forth in the 35 U.S.C. 101 rejection. A 35 U.S.C. 112, first paragraph, rejection should be imposed or maintained when an appropriate basis exists for imposing a rejection under 35 U.S.C. 101.

Claims 14–17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants argue that the PTO has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention; that a specification teaching how to make and use the claimed subject matter must be taken as being in compliance with the enablement requirement unless there is a reason to doubt the objective truth of the statements contained therein which are relied on for enabling support; that the PTO's fail to meet this burden because they are fundamentally flawed for at least two reasons; that first, the PTO is relying on a definition of the term "active" or "activity" found in the specification; that however, the claims at issue do not use the terms "active" or "activity;" that the PTO is impermissibly importing a limitation into the claims from the specification; that second, even if the PTO were correct to suggest that the claimed polypeptides of claims 14-17 were required to be "active," nothing in the quoted portion of the specification suggests that the "specification intends immunologically active peptides to also retain biological activity of a native or naturally-occurring PRO" as the PTO suggests; that even if Applicants have failed to disclose the "biological" activity of the PRO polypeptide as the PTO asserts, this is not relevant to the enablement of the claims at issue because: (1) the claims do not recite the defined terms "active," "activity," "biological activity" or "immunological activity;" and (2) nothing in the specification requires immunologically active polypeptides to also be "biologically active." Applicants' arguments have been fully considered but they are not persuasive. As indicated previously, all questions of enablement are evaluated against the claimed subject matter. The focus of the examination inquiry is whether everything within the scope of the claim is enabled. Accordingly, the first analytical step requires that the examiner determine exactly what subject matter is encompassed by the claims. The claims require "said isolated polypeptide or a

fragment thereof ... to generate an antibody." The examiner reasonably construes this requirement as "immunological activity." The specification clearly construes polypeptides having an "immunologically activity" as also retaining "a biological function (either inhibitory or stimulatory) caused by a native or naturally-occurring PRO." It is applicants that would have the examiner impermissibly limit the claims to immunologically active, but not biologically active peptides.

Applicants argue that Claims 14-17 do not require that the variant polypeptides of Claims 14-17 are capable of generating antibodies which bind the polypeptide of SEQ ID NO:110 without binding to the variant polypeptides themselves; that the subject matter within the scope of Claims 14-17 includes variant polypeptides which can be used to generate antibodies which bind to both the variant polypeptide used to generate them and to the polypeptide of SEQ ID NO: 110, but which antibodies "can be used to specifically detect the polypeptide of SEQ ID NO: 110 in esophageal tissue samples;" that the PTO will appreciate that, in view of the high degree of homology between the polypeptides of Claims 14-17 and the polypeptide of SEQ ID NO:110, there are many antibodies which will bind to both polypeptides and, accordingly, the polypeptides of Claims 14-17 are useful for producing antibodies which can be used as diagnostic agents for detecting the polypeptide of SEQ ID NO: 110 in a sample; that as all of the PTO's arguments attempting to establish a reasonable basis to question the enablement provided for the claimed invention are fundamentally flawed, the PTO has again failed to provide sufficient evidence to support a prima facie rejection of Claims 14-17; that a specification teaching how to make and use the claimed subject matter must be taken as being in compliance with the enablement requirement unless there is a reason to doubt the objective truth of the

statements contained therein which are relied on for enabling support; that the specification teaches in detail how to make the claimed polypeptides, including variants thereof, and antibodies which specifically bind PRO1753; that the specification discloses that antibodies to claimed polypeptides can be used in diagnostic assays to detect the expression of PRO1753 in specific types of tissue; that thus, there is significant guidance how to make and use the claimed polypeptides; that as the disclosure and references cited in the specification make clear, the production of polypeptides, polypeptide variants, and specific antibodies is a predictable and well established aspect of the biological sciences, citing Sutcliffe (Science (1983) 219:660-666 at 661-662) (teaching that "by following simple rules, one can in general select peptides that will elicit antibodies reactive with intact proteins"); that the PTO's rejection based on lack of utility has been addressed above, and the PTO has otherwise failed to meet its burden to establish a reasonable basis to question the enablement provided for the claimed invention; that given the skill in the art and the disclosure of how to make and use the claimed polypeptides, Applicants request that the PTO reconsider and withdraw its rejection under 35 U.S.C. § 112, first paragraph.

Applicants' arguments have been fully considered but they are not persuasive. Sutcliffe (Science (1983) 219:660-666 at 661-662) is not commensurate with the claimed invention because Sutcliffe does not teach making a variant of a peptide in order to use the variant to make an antibody to the peptide. Sutcliffe teaches selecting a peptide sequence from the native sequence. The state of the art, as evidenced by Sutcliffe, is that one does not make a variant of peptide in order to make antibodies that bind the peptide.

As noted by applicants, the claims require antibodies that "can be used to specifically detect the polypeptide of SEQ ID NO: 110 in esophageal tissue samples." However, the specification defines antibody specificity as follows:

> An antibody that "specifically binds to" or is "specific for" a particular polypeptide or an epitope on a particular polypeptide is one that binds to that particular polypeptide or epitope on a particular polypeptide without substantially binding to any other polypeptide or polypeptide epitope. Page 42, paragraph 0247.

The state of the art is such that one does not typically make a variant of polypeptide in order to make antibodies that bind the polypeptide without substantially binding the variant. The obvious choice is to use the polypeptide itself. The level of ingenuity required to make such an invention is clearly beyond that to be expected of skilled artisans. The specification does not disclose how this would be accomplished.

Claims 14–17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants argue that to overcome the presumption that the claimed subject matter is adequately described, the PTO must present "evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims; that to support its rejection of pending Claims 14-17, the PTO has merely repeated, nearly verbatim, the same arguments made in support of its enablement rejection; that for the reasons discussed above, these arguments are fundamentally flawed because the mischaracterize the claimed subject matter; that as noted previously, "[a] description as filed is presumed to be adequate,

unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption." M.P.E.P. § 2163.04 (emphasis added). Therefore "[t]he examiner has the initial burden of presenting by a preponderance of evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims." Id.; that the arguments fail to meet this burden because they are fundamentally flawed for at least two reasons; that first, the PTO is relying on a definition of the term "active" or "activity" found in the specification; that however, the claims at issue do not use the terms "active" or "activity."; that therefore, the PTO is impermissibly importing a limitation into the claims from the specification; that second, even if the PTO were correct to suggest that the claimed polypeptides of claims 14-17 were required to be "active," nothing in the quoted portion of the specification suggests that the "specification intends immunologically active peptides to also retain biological activity of a native or naturally-occurring PRO" as the PTO suggests; that applicants clearly contemplated that "biological" activity was distinct from "immunological" activity; that in addition, according to the PTO, the specification teaches that "'Active' or 'activity' for the purposes herein refers to form(s) of a PRO polypeptide which retain a biological and/or an immunological activity of native or naturally-occurring PRO."; that clearly, Applicants contemplated that an "active" polypeptide can have "biological activity" or "immunological activity."; that thus, the specification clearly teaches that a PRO polypeptide can retain "biological" activity, which does not include immunological activity, "immunological" activity, which does not include biological activity, or both; that therefore, even if Applicants have failed to disclose the "biological" activity of the PRO polypeptide as the PTO asserts, this is not relevant to the written description of the claims at issue because: (1) the claims do not recite

the defined terms "active," "activity," "biological activity" or "immunological activity;" and (2) nothing in the specification requires immunologically active polypeptides to also be "biologically active." Applicants' arguments have been fully considered but they are not persuasive. The claims require "said isolated polypeptide or a fragment thereof ... to generate an antibody." The examiner reasonably construes this requirement as "immunological activity." The specification clearly construes polypeptides having an "immunologically activity" as also retaining "a biological function (either inhibitory or stimulatory) caused by a native or naturally-occurring PRO." Therefore, the claims encompass any and all antigenically cross-reactive polypeptides possessing the recited percent identity to the amino acid sequence of SEQ ID NO: 110, and possessing any and/or all underlying biological activities. However, the specification does not describe any biological activity of the native or naturally-occurring PRO1753 polypeptide SEQ ID NO: 110. Therefore, skilled artisans would not recognize the disclosure of SEQ ID NO: 110 as putting applicants in possession of the claimed genus. It is applicants that would have the examiner impermissibly limit the claims to immunologically active, but not biologically active peptides.

Applicants argue that the PTO also argues that making claimed variants is not as predictable as making nucleic acids that encode a particular amino acid sequence because "the claimed variant polypeptides are all different polypeptides ... that vary anywhere and everywhere from SEQ ID NO: 110, within the metes and bounds of the recited percent identity."; that the PTO also argues that unlike biological activity, the function of being used to generate an antibody to specifically detect the polypeptide of SEQ ID NO: 110 does not limit the claimed variants in any discernable, predictable or disclosed manner; that these arguments do not address

the teaching of the In re Wallach case and Example 14 of the Written Description Guidelines; that the Wallach case states that "we see no reason to require a patent applicant to list every possible permutation of the nucleic acid sequences that can encode a particular protein for which the amino acid sequence is disclosed, given the fact that it is, as explained above, a routine matter to convert back and forth between an amino acid sequence and the sequences of the nucleic acid molecules that can encode it." In re Wallach, 378 F.3d 1330, 1333-34 (Fed. Cir. 2004) (emphasis added); that likewise, it is a routine matter to generate the list of polypeptides which have either 95% or 99% amino acid with SEQ ID NO: 110 as disclosed in the specification; that example 14 discloses that there is sufficient written description where a percent sequence identity is recited to a disclosed sequence, and a test is disclosed to determine if the variant polypeptide posses the function of the disclosed sequence; that there in nothing in Example 14 that requires that the recited function limit the structure of the variant protein in any "discernable, predictable or disclosed manner."; that here, Applicants have recited the function "wherein said isolated polypeptide or a fragment thereof can be used to generate an antibody which can be used to specifically detect the polypeptide of SEQ ID NO: 110 in esophageal tissue samples."; that based on the disclosure of the application as filed and the skill in the art, a skilled artisan can test variant polypeptides to determine if they retain this function. Applicants' arguments have been fully considered but they are not persuasive. The examiner believes he has adequately addressed the teaching of the In re Wallach case and Example 14 of the Written Description Guidelines. The In re Wallach case found that the complete amino acid sequence of a particular protein may put inventor in possession of genus of DNA sequences encoding it, and a person of ordinary skill in art may therefore have been in possession of entire genus of DNA

sequences that can encode disclosed partial protein sequence. The Wallach case further found that it is routine matter to convert back and forth between amino acid sequence and sequences of nucleic acid molecules that can encode it. However, in the present case applicants are claiming a genus of variant polypeptides that can be used to generate an antibody that specifically detects the PRO1753 polypeptide in esophageal tissue samples. Thus, the Wallach case is distinguishable on the facts because one does not typically convert back and forth between variant amino acid sequences and the sequence of the native polypeptide in order to generate antibodies that specifically detect the native polypeptide. One uses the native polypeptide itself. The examiner did not require applicants to list every possible permutation of the claimed genus.

A biological activity imposes limitations on the nature, type and number of amino acid changes. However, the functional property of "can be used to generate an antibody ... to specially detect the polypeptide of SEQ ID NO: 110" does not limit the variation in the structure of the claimed variants in any discernable, predictable or disclosed manner. This distinguishes the claimed invention from Example 14. The examiner did not say that example 14 requires that the recited function limit the structure of the variant protein in any "discernable, predictable or disclosed manner."

Applicants argue that claims 14-17 do not require that the variant polypeptides of Claims 14-17 are capable of generating antibodies which bind the polypeptide of SEQ ID NO:110 without binding to the variant polypeptides themselves; that rather, the subject matter within the scope of Claims 14-17 includes variant polypeptides which can be used to generate antibodies which bind to both the variant polypeptide used to generate them and to the polypeptide of SEQ ID NO:ll0, but which antibodies "can be used to specifically detect the polypeptide of SEQ ID

NO: 110 in esophageal tissue samples."; that indeed, the PTO will appreciate that, in view of the high degree of homology between the polypeptides of Claims 14-17 and the polypeptide of SEQ ID NO: 110, there are many antibodies which will bind to both polypeptides and, accordingly, the polypeptides of Claims 14-17 are useful for producing antibodies which can be used as diagnostic agents for detecting the polypeptide of SEQ ID NO: 110 in a sample. Applicants' arguments have been fully considered but they are not persuasive. As noted by applicants, As noted by applicants, the claims require antibodies that "can be used to specifically detect the polypeptide of SEQ ID NO: 110 in esophageal tissue samples." However, the specification defines antibody specificity as follows:

> An antibody that "specifically binds to" or is "specific for" a particular polypeptide or an epitope on a particular polypeptide is one that binds to that particular polypeptide or epitope on a particular polypeptide without substantially binding to any other polypeptide or polypeptide epitope. Page 42, paragraph 0247.

The state of the art is such that one does not typically make a variant of polypeptide in order to make antibodies that bind the polypeptide without substantially binding the variant. The obvious choice is to use the polypeptide itself. Therefore, the function of the claimed variants is not related to the structure of the claimed variants. Therefore, skilled artisans would not recognize the disclosure of SEQ ID NO: 110 as putting Applicants in possession of the claimed genus.

Conclusion

No claims are allowable.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under

37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (571) 272-0890. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 9:00 A.M. TO 5:30 P.M. IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, BRENDA BRUMBACK, CAN BE REACHED ON (571) 272-0961.

IF SUBMITTING OFFICIAL CORRESPONDENCE BY FAX, APPLICANTS ARE ENCOURAGED TO SUBMIT OFFICIAL CORRESPONDENCE TO THE CENTRAL FAX NUMBER FOR OFFICIAL CORRESPONDENCE, WHICH IS (571) 273-8300.

CUSTOMERS ARE ALSO ADVISED TO USE CERTIFICATE OF FACSIMILE PROCEDURES WHEN SUBMITTING A REPLY TO A NON-FINAL OR FINAL OFFICE ACTION BY FACSIMILE (SEE 37 CFR 1.6 AND 1.8).

ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING MAY BE OBTAINED FROM THE PATENT APPLICATION INFORMATION RETRIEVAL (PAIR) SYSTEM. STATUS INFORMATION FOR PUBLISHED APPLICATIONS MAY BE OBTAINED FROM EITHER PRIVATE PAIR OR PUBLIC PAIR. STATUS INFORMATION FOR UNPUBLISHED APPLICATIONS IS AVAILABLE THROUGH PRIVATE PAIR ONLY. FOR MORE INFORMATION ABOUT THE PAIR SYSTEM, SEE HTTP://PAIR-DIRECT.USPTO.GOV. CONTACT THE ELECTRONIC BUSINESS CENTER (EBC) AT 866-217-9197 (TOLL-FREE) FOR QUESTIONS ON ACCESS TO THE PRIVATE PAIR SYSTEM,

DAVID ROMEO
PRIMARY EXAMINER
ART UNIT 1647

DSR
FEBRUARY 7, 2007